



Title	Reduction in anxiety during treatment with exercise and duloxetine is related to improvement of low back pain-related disability in patients with non-specific chronic low back pain
Author(s)	Onda, Akira; Kimura, Masashi
Citation	Fukushima Journal of Medical Science. 66(3): 148-155
Issue Date	2020
URL	<a href="http://ir.fmu.ac.jp/dspace/handle/123456789/1358">http://ir.fmu.ac.jp/dspace/handle/123456789/1358</a>
Rights	© 2020 The Fukushima Society of Medical Science. This article is licensed under a Creative Commons [Attribution-NonCommercial-ShareAlike 4.0 International] license.
DOI	10.5387/fms.2020-22
Text Version	publisher



## Reduction in anxiety during treatment with exercise and duloxetine is related to improvement of low back pain-related disability in patients with non-specific chronic low back pain

Akira Onda and Masashi Kimura

*Department of Orthopaedic Surgery, Zenshukai Hospital, Maebashi City, Gunma, Japan*

(Received September 17, 2020, accepted November 18, 2020)

### Abstract

**Background :** Non-invasive treatment is generally recommended for patients with non-specific chronic low back pain (CLBP). However, the impact of combination therapy with physical exercise and a serotonin-norepinephrine reuptake inhibitor has not been clarified in patients with non-specific CLBP. This study assessed the efficacy of combination treatment with exercise and duloxetine on non-specific CLBP and aimed to identify factors that contributed to improvement of LBP-induced disability.

**Methods :** This prospective study was conducted on consecutive outpatients with non-specific CLBP. Patients received a supervised home-based exercise program and duloxetine administration for 15 weeks. The Roland-Morris Disability Questionnaire (RDQ), Numerical Rating Scale (NRS), Hospital Anxiety and Depression Scale (HADS), and Pain Catastrophizing Scale (PCS) were assessed at baseline and 15 weeks. Multiple logistic regression modeling was used to identify factors associated with an improvement in RDQ.

**Results :** Forty-two patients were enrolled. Overall, scores on the RDQ, NRS, and PCS (total score, magnification, helplessness) were significantly reduced at 15 weeks ( $p < 0.01$  for all). An improvement of disability was confirmed in 22 patients (52%). A higher HADS depression score before and after the intervention was significantly associated with a lack of improvement in disability ( $p < 0.01$ ). Further, a reduction in HADS anxiety score over 15 weeks was a significant factor associated with an improvement in disability (odds ratio : 1.99 ; 95% CI : 1.26-3.65).

**Conclusions :** Supervised exercise plus duloxetine resulted in favorable outcomes and an improvement of LBP-related disability in approximately 50% of patients. A reduction in anxiety over treatment was associated with the improved disability.

**Key words :** non-specific chronic low back pain, disability, duloxetine, physical exercise

### Introduction

Chronic low back pain (CLBP) is a major health problem worldwide, with a lifetime prevalence of about 23%, and 11-12% of the population becoming disabled<sup>1)</sup>. This persistent painful condition is associated with the development of multiple physical and psychosocial disabilities. Thus, strategies that focus on impaired physical activities as well as pain

improvement are important in the treatment of CLBP.

Non-specific CLBP is defined as CLBP not attributable to a recognizable, known pathoanatomical cause. Systematic reviews of randomized controlled trials have reported on outcomes associated with various intervention strategies<sup>2-4)</sup>. It is generally recommended that patients are treated with non-invasive interventions, including physical exer-

Corresponding author : Akira Onda, MD, PhD E-mail : onda@zenshukai.com

©2020 The Fukushima Society of Medical Science. This article is licensed under a Creative Commons [Attribution-NonCommercial-ShareAlike 4.0 International] license.  
<https://creativecommons.org/licenses/by-nc-sa/4.0/>

cise, cognitive-behavioral therapy, patient education, mental healthcare, and use of therapeutic agents for non-specific CLBP. However, such interdisciplinary approaches usually take place in a limited number of facilities for patients with intractable chronic pain.

Exercise programs have been found to be effective at reducing pain, improving physical function, and helping people return to work<sup>2,5,6</sup>. It has also been demonstrated that most exercise programs consist of individually designed, supervised programs, such as home-based exercises with regular follow-up visits to physical therapists<sup>7</sup>. In terms of pharmacologic therapies, oral non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are used worldwide in the treatment of CLBP. However, long-term use of NSAIDs is associated with renovascular, cardiovascular, and gastrointestinal risks. Thus, the lowest effective dose of an NSAID for the shortest period is recommended<sup>4</sup>. Strong opioids are generally considered a last resort due to the potential for misuse, abuse, or addiction and should be reserved for cases in which all other pharmacological options or alternative treatments have failed<sup>4</sup>. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is a unique analgesic that has recently been recognized to be an effective agent for treatment of CLBP without causing serious adverse effects<sup>8,9</sup>. Its pharmacological effects occur via modulation of the descending pain pathway, which is dysfunctional in patients with chronic pain conditions<sup>10</sup>. This mechanism, along with its good safety profile, lead us to believe that duloxetine may be better than conventional analgesics in patients with CLBP.

It is therefore plausible that supervised physical exercise plus duloxetine could be a potentially optimal treatment strategy in the primary outpatient setting. However, most systematic reviews highlighted the effectiveness of a single intervention; few studies have assessed combination therapies of different types in patients with CLBP. We suggest that a combination of physical exercise and medication with proven benefits is a feasible and reasonable strategy for patients with disabling CLBP. The primary objectives of this study were to assess the impact of combination therapy with supervised physical exercise and duloxetine administration on pain, disability, and psychologic distress and to identify factors that contribute to the alleviation of disability in patients with non-specific CLBP.

## Materials and Methods

### *Participants and study design*

This prospective study included consecutive patients diagnosed with non-specific CLBP at a single hospital between February 2017 and February 2019. Eligible patients were adults aged 30 to 79 years who presented to our department with CLBP of at least 3 months' duration. LBP was defined as a pain localized below the costal margin and above the inferior gluteal folds without symptoms of radicular leg pain or numbness. The diagnosis was made by an orthopedic surgeon certified by the Japanese Orthopaedic Association and the Japanese Society for Spine Surgery and Related Research. Plain radiographs and magnetic resonance imaging were used to assist in the diagnosis. Exclusion criteria included malalignment of the lumbar spine, spondylolysis, spondylolisthesis, disc herniation, infection, spinal compression fracture, and tumor. Spinal malalignment was defined as a coronal curvature  $\geq 10^\circ$  Cobb angle or PI (pelvic incidence) - LL (lumbar lordosis)  $\geq 10^\circ$  while standing. Subjects were also excluded if they had a history of previous lumbar spine surgery; severe cardiovascular, hepatic, or renal disorders; pregnancy; gait disturbance requiring crutches or a walker; any type of treatment for LBP within 1 month before the first visit; cognitive impairment with obvious difficulty for self-reported questionnaires; and a history of psychogenic disorders. Assessment for existence of psychological disorders was not conducted for study entry at first visit. The study protocol was approved by the institutional review board of our hospital (No. 17020101) and registered at a national clinical trial site (UMIN 000039713). We humbly confess delayed registration of this clinical trial, in part due to a lack of knowledge about registration protocols. Written informed consent was obtained from all eligible participants.

### *Interventions*

#### Physical exercise

Rehabilitation and home exercise advice for self-care were provided by physiotherapists on a 1-to-1 basis at the rehabilitation department's outpatient service. The exercise program focused on trunk muscle stretching and strengthening and was supplemented by a light aerobic warm-up such as on a stationary bicycle or treadmill. Stretching exercises included a series of 5 static stretches focused on the abdominal and low back muscles, iliopsoas,

gluteal muscles, and hamstrings. Strengthening exercises consisted of maneuvers of abdominal draw-in for trunk flexors, and bridge and bird-dog for trunk extensors. Patients were required to attend the program once a week or once in 2 weeks and advised to continue exercises at home for 15 weeks. Home exercises consisted of 3 to 5 sets of 5 to 10 repetitions for each aforementioned stretching and strengthening activity; patients were encouraged to perform the exercises twice daily based on their ability. A brochure that featured pictures of each exercise was given to each patient to serve as a reminder of how to perform the exercises.

#### Duloxetine

Oral administration of duloxetine started from 20 mg at bedtime for 1 week and increased to 40 mg after 1 week and then to a maximum of 60 mg over 15 weeks. The maintenance dosage was adjusted individually with a flexible dosing approach, considering patients' preferences and minimizing adverse drug reactions. Metoclopramide 5 mg/day was also administered prophylactically to reduce symptoms of nausea that could be caused by duloxetine. Participants underwent tapering of duloxetine after 15 weeks. Additional therapies for pain relief excluding physical exercise were prohibited during the study.

#### Clinical outcome measurements

Clinical assessments were conducted by self-reported questionnaires distributed by the nurse in charge of patients at the outpatient clinic before treatment and at 15 weeks after treatment. The Roland-Morris Disability Questionnaire (RDQ), which is recognized worldwide as a measurement of physical disability associated with activities of daily living (ADL) due to LBP<sup>11)</sup>, was completed by all participants at both time points. The RDQ contains 24 items that are not weighted, and scores range from 0 (no disability) to 24 (maximum disability). Higher scores indicate higher LBP-induced disability regarding ADL. A reduction in score of >2 points at 15 weeks was determined to represent a clinically meaningful improvement in ADL<sup>12)</sup>. Based on this criteria, the participants were categorized into 2 groups: responders (R) and non-responders (non-R).

Pain intensity was assessed using a numerical rating scale (NRS) for worst pain experienced during the past week. Scores were assessed on an 11-point scale, where 0 = no pain and 10 = worst imaginable pain. The Hospital Anxiety and Depression

Scale (HADS) was used to evaluate the severity of anxiety and depression. The HADS contains 14 items, 7 of which relate to anxiety (HADS-A) and 7 of which related to depressive symptoms (HADS-D). Each item is scored from 0 to 3, and the total score ranges from 0 to 21. Higher scores indicate the presence of anxiety and/or depression. A score between 0 and 7 represents the absence of anxiety or depression; a score between 8 and 10 suggests possible anxiety or depression; a score  $\geq 11$  indicates clinically significant anxiety or depression<sup>13,14)</sup>. Pain catastrophizing was measured with the Pain Catastrophizing Scale (PCS), which contains 13 items related to 3 factors: rumination (5 items), magnification (3 items), and helplessness (5 items). Each item is scored from 0 to 4, and the total PCS score ranges from 0 to 52. Higher scores indicate a greater level of pain catastrophizing.

#### Statistical analysis

The per-protocol analysis population included all subjects who completed the study protocol. Continuous variables are presented as mean  $\pm$  SD. Categorical variables are presented as numbers. Demographic data were assessed using the  $\chi^2$  test and the unpaired t-test. Differences in scores on NRS, HADS, and PCS between baseline and 15 weeks were assessed using the Wilcoxon signed-ranks test. The Mann-Whitney test was used for comparisons between the R and non-R groups. Variables with  $p$  values  $<0.1$ , which could represent factors involved in the improvement of disability, were assessed as independent variables by a simultaneous multivariate logistic regression analysis. Outcomes were reported as odds ratios (OR) with 95% confidence intervals (CI). A  $p$ -value  $<0.05$  was considered statistically significant. Data were analyzed with JMP<sup>®</sup> software (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 42 patients (22 men and 20 women; mean age,  $62.6 \pm 13.9$  years) of 51 enrolled were included in the per-protocol analysis. A mean duration of symptoms was  $27.4 \pm 18.5$  months. Reasons for discontinuation were as follows: lost to follow-up ( $n = 4$ ), nausea ( $n = 2$ ), somnolence ( $n = 1$ ), headache ( $n = 1$ ), and appetite loss ( $n = 1$ ), including 9.8% ( $n = 5$ ) duloxetine-induced adverse reactions (Figure 1). No serious adverse events occurred throughout the study. In terms of duloxetine dose, 15 patients received 20 mg/day, 17 pa-

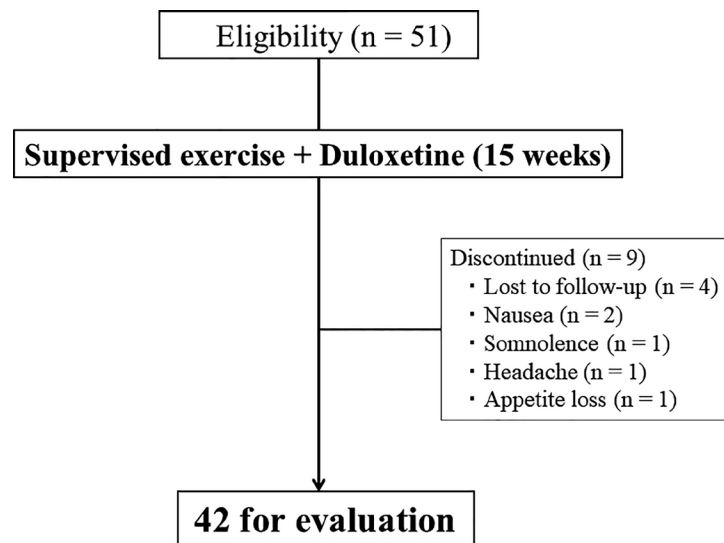


Figure 1. Study flow diagram

Of 51 eligible participants, four were lost to follow-up and five discontinued because of adverse effects of duloxetine. The remaining 42 participants completed this study.

tients received 40 mg/day, and 10 patients received 60 mg/day.

#### *Efficacy of combined treatment*

The RDQ and NRS scores were significantly reduced at 15 weeks ( $p < 0.01$  for both; Table 1). Psychological measurements showed that total PCS score, magnification score, and helplessness score were significantly reduced compared with baseline ( $p < 0.01$  for all). Neither HADS-A nor HADS-D changed after the intervention.

Improvement of ADL by RDQ score was seen in 22 patients (52%, group R); the remaining 20 pa-

tients (group non-R) did not show any changes. No significant differences in demographic characteristics were seen between the R and non-R groups (Table 2). HADS-D scores in the non-R group were significantly higher than those in the R group before and after the intervention ( $p < 0.01$ ; Table 3). In terms of the changes in scores after intervention (pre-post), a significant difference was found only in the HADS-A score in comparisons of groups ( $p < 0.01$ ). There was a modest but insignificant difference in NRS score between groups ( $p = 0.06$ ). The multivariate regression analysis, where HADS-A and NRS scores were considered independent variables based on results of univariate analyses, revealed that a reduction in HADS-A score was a contributing factor for the improvement of LBP-induced disability (OR : 1.99, 95% CI : 1.26-3.65, C statistic : 0.82;  $p < 0.01$ ; Table 4).

Table 1. Overall treatment outcomes ( $n = 42$ )

	Pre	Post	<i>P</i>
RDQ	7.8 ± 2.8	5.9 ± 3.1	<0.01
NRS	6.0 ± 1.3	4.6 ± 2.1	<0.01
PCS			
total score	26.9 ± 9.8	23.2 ± 10.1	<0.01
rumination	13.4 ± 4.8	12.0 ± 4.0	0.09
magnification	5.5 ± 2.7	4.3 ± 2.4	<0.01
helplessness	8.1 ± 3.3	6.8 ± 3.8	<0.01
HADS			
anxiety	6.8 ± 3.9	6.8 ± 3.6	0.78
depression	5.6 ± 2.8	5.5 ± 3.2	0.67

Notes : Values are presented as means ± standard deviation

Abbreviations : RDQ, Roland-Morris Disability Questionnaire; NRS, Numerical Rating Scale; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale.

Table 2. Comparisons of demographic data between groups

	R	Non-R	<i>P</i>
Age (years)	63.6 ± 12.5	61.5 ± 15.4	0.62
Gender (M/F)	12/10	10/10	0.77
BMI (kg/m <sup>2</sup> )	25.7 ± 3.8	24.6 ± 3.3	0.33
Duration of symptoms, months (range)	26.0 ± 20.4 (3-60)	28.9 ± 16.4 (6-60)	0.61

Notes : Variable data : mean ± standard deviation; categorical data : number of cases

Abbreviations : R, group of responders; Non-R, group of non-responders; BMI, body mass index.

Table 3. Comparisons of changes in scores between groups

		R	Non-R	P	Difference (pre-post)		
					R	Non-R	P
<b>NRS</b>	pre	6.1 ± 1.0	5.9 ± 1.6	0.99			
	post	4.2 ± 1.7	5.1 ± 2.4	0.15	1.9 ± 1.9	0.8 ± 2.1	0.06
<b>PCS</b>							
total score	pre	25.9 ± 11.4	28.0 ± 7.8	0.47			
	post	22.2 ± 9.9	21.4 ± 10.4	0.41	3.7 ± 5.8	3.7 ± 8.9	0.72
rumination	pre	13.3 ± 4.8	13.5 ± 4.9	0.80			
	post	12.0 ± 3.4	12.0 ± 4.8	0.94	1.2 ± 2.7	1.5 ± 6.1	0.87
magnification	pre	5.3 ± 2.8	5.8 ± 2.6	0.53			
	post	3.8 ± 2.7	4.8 ± 1.9	0.23	1.5 ± 1.7	1.0 ± 1.5	0.27
helplessness	pre	7.6 ± 3.7	8.7 ± 2.7	0.45			
	post	6.5 ± 3.9	7.1 ± 3.7	0.59	1.2 ± 2.8	1.6 ± 2.0	0.69
<b>HADS</b>							
anxiety	pre	6.8 ± 3.8	6.8 ± 4.1	0.97			
	post	6.0 ± 3.1	7.7 ± 4.0	0.24	0.8 ± 1.7	-1.0 ± 1.5	<0.01
depression	pre	4.2 ± 2.2	7.1 ± 2.7	<0.01			
	post	3.7 ± 2.4	7.5 ± 2.9	<0.01	0.5 ± 1.8	-0.35 ± 2.4	0.17

Notes : Values are presented as means ± standard deviation

Abbreviations : R, group of responders ; Non-R, group of non-responders ; NRS, Numerical Rating Scale ; PCS, Pain Catastrophizing Scale ; HADS, Hospital Anxiety and Depression Scale.

Table 4. Factors associated with improvement of disability in logistic regression analysis

Factor	Regression coefficients (β)	SE	Odds ratio (95% CI)	P
d-NRS	0.24	0.19	1.27 (0.89-1.89)	0.20
d-HADS anxiety	0.69	0.27	1.99 (1.26-3.65)	<0.01

Notes : C statistic : 0.82

Abbreviations : d-NRS, difference in Numerical Rating Scale ; d-HADS, difference in Hospital Anxiety and Depression scale ; SE, standard error. CI, confidence interval.

## Discussion

Though various therapeutic strategies are available for CLBP, non-invasive interventions for non-specific CLBP are preferred. Evidence based on meta-analyses and systematic reviews suggests that physical exercise alone has a positive influence on pain intensity, ADL, physical function, and psychological impairment<sup>2,6,15</sup>. Reduced scores in NRS and RDQ after intervention in this study support findings in these studies. A reduction in PCS score was seen in this study after intervention as well, and low levels of physical activity are closely related to high pain catastrophizing and fear-avoidance beliefs<sup>16,17</sup>. On the other hand, mental scores of anxiety and depression, which are common comorbidities

in patients with persistent pain conditions such as CLBP<sup>18,19</sup>, were relatively low to begin with and did not improve throughout the study as a whole.

Based on its efficacy and safety, duloxetine was used in this study to replace NSAIDs or opioids including tramadol due to the potential adverse effects of these agents<sup>10</sup>. Duloxetine is approved by the Food and Drug Administration for diabetic neuropathic pain, fibromyalgia, major depressive disorder, generalized anxiety disorder, and chronic musculoskeletal disorder and has been used for the same indications except for generalized anxiety disorder in Japan. It is reported that duloxetine substantially reduces pain by acting directly on pain modulation rather than lifting depressive symptoms in patients with CLBP<sup>20</sup>. This underlying mechanism seems



to be due to activation of the descending inhibitory pain pathway, which leads to normalization of the dysfunctional process, a finding that is supported in rat neuropathic pain models<sup>21,22</sup>. The observed reduction in pain intensity might be partially explained by the duloxetine-induced analgesic effect, independent of its antidepressant and anxiolytic effects. The most common adverse reactions associated with duloxetine include nausea, somnolence, dizziness, constipation, and dry mouth, most of which are mild or moderate in severity and occur in the initial phase of administration<sup>8,23</sup>. Adverse events leading to discontinuation in this study were observed in 5 patients (9.8%), and this occurrence was lower than values reported in a double-blind, randomized controlled study (13.9% for duloxetine 60–120 mg/day vs 5.8% for placebo)<sup>23</sup>. The lower rate of adverse events may be due to the lower dosing of 20–60 mg/day in this study and the concomitant administration of metoclopramide.

Importantly, understanding characteristics of patients with CLBP should focus not only on pain but also on the impact of disability or interference with daily activities. One study reported a disassociation between severity of pain and disability in almost half of patients with LBP in which participants with a high level of disability despite only mild pain were older, felt more stress, were more depressed, and were less satisfied with working conditions compared with those with the opposite pattern<sup>24</sup>. Furthermore, regardless of pain intensity, a significant association between RDQ score and medical care visit (medical clinic or complementary/alternative medical clinic) was reported in the patients with LBP<sup>25</sup>. Consequently, an exploration of factors associated with an improvement of LBP-induced disability allowed us to identify a potential therapeutic target. In the current study, changes in NRS resulted in a small, insignificant association with an improvement of disability. This finding is thought to partly reflect the aforementioned potential disassociation between LBP and disability. Interestingly, our results showed that only a reduction in anxiety during treatment was associated with amelioration of disability. This fact implies that anxiolytic care might be a crucial element of treatment when physical activities are impaired. In contrast, about half of our patients did not show any improvement in disability, and these patients had pronounced higher scores in depression at baseline compared with those with improvement in disability. This tendency lasted until endpoint, indicating that the treatment strategy failed to reduce depressive symp-

toms. The finding that therapeutic effects in the context of comparatively high scores in depression were hardly detectable might partly arise from the flexible dosing of duloxetine in the current study. Indeed, an average dose of 37.6 mg/day was lower than the fixed dose of 60 mg/day in previous studies in which duloxetine led to an improvement of depression score in the patients with CLBP<sup>20,26</sup>. It is well known that symptoms of depression are associated with poor prognosis regarding pain intensity, disability, health-related quality of life, chronicity, and labor productivity<sup>27–29</sup>. For selected patients with suspected or clinically significant depressive symptoms at the first visit, early intervention using a multidisciplinary approach with cognitive-behavioral therapy might be superior to the treatment used in the current study.

Our study has some limitations. First, there was no control group for combined treatments. Exercise therapies and medication are often provided at the same time for CLBP rather than monotherapy in orthopaedic clinics. Accordingly, prospective randomized studies comparing exercise plus duloxetine and exercise plus other pain-killers including weak opioids might be warranted to validate the benefit of duloxetine treatment. Second, adherence to prescribed home exercises was not investigated, and good adherence is considered to be associated with better clinical outcomes. Third, the treatment period was relatively short, and definitive outcomes for CLBP require long-term observations. Finally, symptom duration was 2.3 years on average in this study. It was reported that patients with  $\geq 3$  years of pain at baseline took a significantly longer time to improve than those with a shorter duration of pain<sup>30</sup>. However, even with these limitations, a combination of supervised exercises, which were continued at home, and duloxetine successfully led to an improvement of pain intensity, LBP-related disability, and pain catastrophizing over 15 weeks. The effectiveness of this combination strategy on disability was seen in approximately half of subjects. The improved LBP-induced disability was relevant to a reduction of anxiety. To our knowledge, the combined therapies of physical exercise and medication for CLBP have seldom been investigated in the last two decades. Considering such a paucity of evidence, these new findings might be meaningful to help develop more appropriate strategies in the treatment of patients with non-specific CLBP.

## Acknowledgments

The authors are grateful to physical therapists at our hospital, especially for Norikazu Kaneko, Natsumi Tsubuko, and Taira Kuroiwa. We also thank the nursing team at our outpatient department for assistance.

## Conflict of Interest Disclosure

The authors declare no conflicts of interest in this work.

## References

- Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*, **379**(9814): 482–491, 2012.
- van Middelkoop M, Rubinstein SM, Kuijpers T, *et al.* A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. *Eur Spine J*, **20**(1): 19–39, 2011.
- Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet*, **389**(10070): 736–747, 2017.
- Schreijenberg M, Koes BW, Lin CC. Guideline recommendations on the pharmacological management of non-specific low back pain in primary care – is there a need to change? *Expert Rev Clin Pharmacol*, **12**(2): 145–157, 2019.
- Oesch P, Kool J, Hagen KB, Bachmann S. Effectiveness of exercise on work disability in patients with non-acute non-specific low back pain: Systematic review and meta-analysis of randomised controlled trials. *J Rehabil Med*, **42**(3): 193–205, 2010.
- Hayden JA, van Tulder MW, Malmivaara AV, Koes BW. Meta-analysis: exercise therapy for nonspecific low back pain. *Ann Intern Med*, **142**(9): 765–775, 2005.
- Hayden JA, van Tulder MW, Tomlinson G. Systematic review: strategies for using exercise therapy to improve outcomes in chronic low back pain. *Ann Intern Med*, **142**(9): 776–785, 2005.
- Konno S, Oda N, Ochiai T, Alev L. Randomized, Double-blind, Placebo-controlled Phase III Trial of Duloxetine Monotherapy in Japanese Patients With Chronic Low Back Pain. *Spine*, **41**(22): 1709–1717, 2016.
- Tsuji T, Itoh N, Ishida M, Ochiai T, Konno S. Response to duloxetine in chronic low back pain: exploratory post hoc analysis of a Japanese Phase III randomized study. *J Pain Res*, **10**: 2157–2168, 2017.
- Smith HS, Smith EJ, Smith BR. Duloxetine in the management of chronic musculoskeletal pain. *Ther Clin Risk Manag*, **8**: 267–277, 2012.
- Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine*, **8**(2): 141–144, 1983.
- Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine*, **25**(24): 3115–3124, 2000.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*, **67**(6): 361–370, 1983.
- Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Psychosom Res*, **52**(2): 69–77, 2002.
- Wegner M, Helmich I, Machado S, Nardi AE, Arias-Carrion O, Budde H. Effects of exercise on anxiety and depression disorders: review of meta-analyses and neurobiological mechanisms. *CNS Neurol Disord Drug Targets*, **13**(6): 1002–1014, 2014.
- Elfving B, Andersson T, Grooten WJ. Low levels of physical activity in back pain patients are associated with high levels of fear-avoidance beliefs and pain catastrophizing. *Physiother Res Int*, **12**(1): 14–24, 2007.
- Grotle M, Vøllestad NK, Veierød MB, Brox JI. Fear-avoidance beliefs and distress in relation to disability in acute and chronic low back pain. *Pain*, **112**(3): 343–352, 2004.
- Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine*, **27**(5): E109–120, 2002.
- Oliveira DS, Vélia Ferreira Mendonça L, Sofia Monteiro Sampaio R, Manuel Pereira Dias de Castro-Lopes J, Ribeiro de Azevedo LF. The Impact of anxiety and depression on the outcomes of chronic low back pain multidisciplinary pain management—a multicenter prospective cohort study in pain clinics with one-year follow-up. *Pain Med*, **20**(4): 736–746, 2019.
- Enomoto H, Fujikoshi S, Funai J, *et al.* Assessment of direct analgesic effect of duloxetine for chronic low back pain: post hoc path analysis of double-blind, placebo-controlled studies. *J Pain Res*, **10**: 1357–1368, 2017.
- Minami K, Tamano R, Kasai E, *et al.* Effects of duloxetine on pain and walking distance in neuropathic pain models via modulation of the spinal



- monoamine system. *Eur J Pain*, **22**(2) : 355-369, 2018.
22. Hoshino H, Obata H, Saito S. Antihyperalgesic effect of duloxetine and amitriptyline in rats after peripheral nerve injury : Influence of descending noradrenergic plasticity. *Neurosci Lett*, **602** : 62-67, 2015.
  23. Skljarevski V, Desai D, Liu-Seifert H, *et al.* Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine*, **35**(13) : E578-585, 2010.
  24. Takahashi N, Kikuchi S, Konno S, *et al.* Discrepancy between disability and the severity of low back pain : demographic, psychologic, and employment-related factors. *Spine*, **31**(8) : 931-939 ; discussion 940, 2006.
  25. Ono R, Yamazaki S, Takegami M, *et al.* Patient-reported disability in the general Japanese population was associated with medical care visits for low back pain, regardless of pain intensity. *J Orthop Sci*, **20**(4) : 742-749, 2015.
  26. Karp JF, Weiner DK, Dew MA, Begley A, Miller MD, Reynolds CF 3rd. Duloxetine and care management treatment of older adults with comorbid major depressive disorder and chronic low back pain : results of an open-label pilot study. *Int J Geriatr Psychiatry*, **25**(6) : 633-642, 2010.
  27. Pinheiro MB, Ferreira ML, Refshauge K, *et al.* Symptoms of depression as a prognostic factor for low back pain : a systematic review. *Spine J*, **16**(1) : 105-116, 2016.
  28. Tsuji T, Matsudaira K, Sato H, Vietri J. The impact of depression among chronic low back pain patients in Japan. *BMC Musculoskelet Disord*, **17**(1) : 447, 2016.
  29. Hung CI, Liu CY, Fu TS. Depression : An important factor associated with disability among patients with chronic low back pain. *Int J Psychiatry Med*, **49**(3) : 187-198, 2015.
  30. Dunn KM, Croft PR. The importance of symptom duration in determining prognosis. *Pain*, **121**(1-2) : 126-132, 2006.